PREVALENCE OF INADEQUATE VITAMIN D INTAKE IN SPINAL MUSCULAR ATROPHY TYPE I POPULATION AS IT CORRELATES WITH BONE HEALTH

by

Jennifer Aton

A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

Division of Nutrition

The University of Utah

August 2011

The University of Utah Graduate School

STATEMENT OF THESIS APPROVAL

The thesis of **Jennifer Aton**

has been approved by the following supervisory committee members:

Kristine Clarke Jordan	, Chair	**5/ 11/2011** Date Approved
Rebecca Hurst Davis	, Member	**5/11/2011** Date Approved
Julie Metos	, Member	**5/11/2011** Date Approved

and by **Eldon Wayne Askew** , Chair of

the Department of **Nutrition**

and by Charles A. Wight, Dean of The Graduate School.

ABSTRACT

Spinal Muscular Atrophy (SMA) is an autosomal recessive disease that causes a degeneration of the anterior horn cells of the spinal cord. SMA Type I is the most severe form, characterized by progressive muscle weakness and atrophy. SMA Type I patients are susceptible to nutritional deficiencies, especially those that correlate to bone health, due to decreased caloric intake and limited weight bearing.

The aim of this study was to evaluate and assess: 1) the adequacy of vitamin D intake as compared to the American Academy of Pediatrics recommendation of 400 IU/day; 2) the correlation between vitamin D intake and associated serum level; and 3) the association between vitamin D and calcium intakes and bone mineral density.

All subjects are participants in an ongoing natural history study at the University of Utah. Participants have a genetic diagnosis of SMA and a clinical diagnosis of Type I. Vitamin D and calcium intakes were assessed with a 3-day food record. Vitamin D serum levels were evaluated from 25-hydroxy vitamin D lab testing. Bone mineral density (BMD) was assessed using Dual Energy X-ray Absorptiometry Scan (DEXA) of the subjects' whole body.

Subjects (n=40) consisted of 22 males and 18 females. The mean age of the subjects was 18.6 months (range 0 to 165 months). Seventy-five percent of patients had an inadequate intake of vitamin D at the initial visit. Vitamin D intake and calcium intake were positively correlated with BMD (r=0.31 and r=0.53, respectively). Increased vitamin D and calcium consumption were associated with an increase in BMD (p=0.04

and p=0.01, respectively). Vitamin D intake correlated positively with serum levels of vitamin D (r=0.65). Within a subset of 14 patients, 71% had a serum vitamin D level in the optimal range.

The majority of patients (75%) reported an inadequate vitamin D intake at their first visit (<400 IU). Inadequate nutrient intake is likely due to the decreased caloric needs of SMA Type I patients. Decreased intake of vitamin D and calcium were associated with a decreased BMD which increases the risk of fractures, scoliosis, and osteoporosis. There continues to be a need for evidence-based research concerning the nutritional needs of SMA Type I patients. Future research involving an experimental study is necessary to determine optimal intakes of vitamin D and calcium in the SMA Type I population.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Funding was provided by SMA Angels, Inc. and in part by NIH grant R01-HD054599 (KJS) from the National Institute of Child Health and Human Development. Additional support was provided by Public Health Services Research Grant UL1-RR025764 and C06-RR11234 (University of Utah) from the National Center for Research Resources and Families of SMA.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by a mutation in the survival motor neuron 1 (SMN1) gene. A corresponding deficiency of the survival motor neuron (SMN) protein causes a degeneration of anterior horn cells in the spinal cord, which leads to progressive muscle atrophy and weakness (1). Severity of the disease is determined by the amount of the SMN2 gene (1).

The most severe form of SMA, Type I, is the leading genetic cause of infant death with an incidence of 1 in 10,000 live births (2). Types of SMA are categorized by age of onset and motor-function achieved (1, 3). Type I, also known as Werdnig-Hoffmann disease, is the most common form of SMA; it is diagnosed before 6 months of age, and 30% of cases are diagnosed prenatally. This form of the disease is rapidly progressive, with a poor prognosis. More recently, due to proactive care, life expectancy may extend past the age of 2 years. In these patients, motor function is impeded by severe hypotonia. For example, affected children are unable to sit unassisted and lack head control (1, 3, 4).

Muscle weakness causes a multitude of problems in the orthopedic, pulmonary, and gastrointestinal systems. Children with SMA are at risk for osteoporosis, fractures, and scoliosis. Restrictive lung disease, due to decreased pulmonary function, is the most common and life-threatening complication specifically in Type I patients (5). Dysphagia, gastrointestinal dysmotility, and constipation are complications associated with muscle weakness in the gastrointestinal system (5). Type I patients commonly experience problems with bulbar denervation, resulting in dysphagia and fatigue, thus increasing the

risk of the patient becoming failure to thrive (FTT). This is a dangerous cycle as feeding problems and constipation increase the risk of poor intake and FTT, which can lead to further weakness and continued feeding problems. Enteral feeds may be required for patients with dysphagia. While FTT is a problem for a proportion of this population, obesity is as well. SMA Type I patients have a lower metabolic rate, due to decreased lean body mass; therefore, excessive weight gain is a concern. Appropriate calories and adequate nutrient intake must be considered when assessing the nutritional needs of a patient with SMA.

Nutritional management is directed toward providing nutritional requirements and improving the quality of life for Type I patients. Although nutrition plays a major role throughout the progression of SMA, there is little research to make a conclusive recommendation for specific nutrient supplementation. The decreased amount of lean body mass and limited activity of SMA Type I patients may translate to a reduced metabolic rate. The daily caloric intake of this population is significantly less than the recommendation for healthy children their age (6). Dietary management requires a balance of calories and nutrients to prevent excess weight gain and undernutrition. Catabolism due to illness, surgery, and undernutrition can be catastrophic in the SMA population as any muscle regression can be permanent. The use of parenteral or enteral nutrition is common when prolonged fasting is anticipated (7).

Although SMA patients have different caloric needs, micronutrient requirements are currently considered to be the same as their age-matched peers. A reduced caloric intake can lead to inadequate micronutrient consumption. SMA Type I patients are particularly susceptible to vitamin D deficiencies, not only because of poor intake, but

also because of decreased movement and drug-nutrient interactions. For example, valproic acid/carnitine, sodium phenylbutyrate, and hydroxyurea are common drug therapies used to treat symptoms of neurological diseases including SMA. These types of treatments can interfere with the absorption of certain micronutrients such as vitamin D (8). SMA children are at greater risk for osteoporosis, fractures and scoliosis; therefore, close monitoring of micronutrients associated with bone health is essential (6, 7, 9). Specifically, a biochemical evaluation of vitamin D status is a key consideration to confirm a deficiency in at-risk patients.

The purpose of this study was to assess the vitamin D intake of a SMA Type I population, as compared to the recommendation from the American Academy of Pediatrics (AAP), 400 IU/day (10). We also evaluated the dietary intake of vitamin D compared to corresponding serum levels and bone mineral density (BMD). We hypothesized that: 1) vitamin D intake of SMA Type I patients is lower than the level suggested by the AAP for children of the same age as a result of a reduced calorie diet; 2) a vitamin D intake lower than the recommendation is associated with a serum level below the ideal range; 3) a suboptimal vitamin D intake is associated with poor bone health indicators. The hypotheses were tested with a 3-day food record, a serum vitamin D test, and a Dual Energy X-ray Absorptiometry (DEXA) scan, respectively.

METHODS

Research Design

This was an observational study of vitamin D intake in Spinal Muscular Atrophy Type I patients. All subjects represented a convenience sample of participants in a natural history study conducted by the Pediatric Motor Disorders Research group at the University of Utah.

Subject Selection Criteria

Potential subjects were participants in an ongoing clinical outcomes trial for SMA Type 1. Inclusion criteria consisted of a clinical diagnosis of Type 1 and a genetic diagnosis of SMA. The mean age of subjects was 18.6 months with a median of 10 months. Participants ranged between 0 months to 165 months in age. Subjects were recruited between June 1, 2001 and February 1, 2011. Written informed parental permission (subjects <18 years) and assent (subjects >7 years) were obtained for all subjects. This study protocol was approved by the Institutional Review Board at the University of Utah.

Data Collection Methods

Dietary Record

At study initiation, parents were asked to complete a 3-day food record for their child. Three-day food records were filled out for each clinic visit. Parents were given a packet explaining how to fill out a record of dietary, fluid, and supplement intake for two

weekdays and one weekend day. For a sample dietary intake form as it appears on the SMA website, see Appendix. The growth parameters of body weight, length, and age were assessed either in a clinic or at home; this information was included with each diet record submission. A food record was submitted by parents in one of three ways: bringing a hand written copy to their clinical visit; entering an online version on the SMA and Nutrition website; or faxing/emailing a copy to the Pediatric Motor Disorders Research group.

The 3-day dietary records were analyzed using ESHA Food Processor (versions 9.1.0 and 10.5.2, ESHA Research, Salem, Oregon) for vitamin D and calcium intake. Vitamin D intake less than 400 IU/day was considered to be deficient; between 400 and 2000 IU was optimal; and greater than 2000 IU was considered a possible toxicity. Vitamin D and calcium intake values were compared to BMD.

From 2009 to present, a dietitian reviewed each dietary analysis and provided feedback to parents. Primarily, the type of diet and formula was chosen by the parent and/or primary care provider. The aim of this study was to evaluate the diet from the initial visit against our outcome variables. Food records were collected for the initial visit from all subjects (n=40). Three-day food records were also collected from patients at each follow-up visit.

Biochemical Measure

A subgroup of subjects had a blood test for serum 25-OH D_3 and serum calcium levels. Subject vitamin D levels were stratified into the following categories: less than 20 ng/mL (deficient), between 20 and 29.9 ng/mL (inadequate), between 30-39.9 ng/mL

(low normal), 40-80 ng/mL (optimal), and greater than 80 ng/mL (high). In addition, vitamin D serum levels were compared to corresponding dietary intake.

Duel-Energy X-ray Absorptiometry Scan

A subgroup of 37 subjects underwent a DEXA scan at each visit to evaluate bone mineral density and bone mineral content. Norland DEXA (XR-36 software version 3.3.1 Fort Atkinson, Wisconsin) for small subjects was used. DEXA has been validated as an appropriate measure of bone mineral density in the target population (12, 13).

Demographic Data

Parents provided demographic data on the parental consent form. Gender and ethnicity were reported for all patients (n=40) and their parents. In addition, the age of the patient was collected on the parental consent form.

Medical History Variables

Parents were asked to report the patient's medical history on the parental consent form. Types of data included family medical history, presence of allergies, medication use, lab results, and physical exam information.

Statistical Methods, Data Analysis, and Interpretation

The Statistical Analysis Software (version 9.1.2, 2010, SAS Institute Inc., Cary, NC, USA) was used to conduct data analyses. A power analysis for the study dependent variable, vitamin D intake, revealed that a sample size of 14 subjects was required to detect a 10% difference from the population mean represented as the AAP recommendation. Vitamin D intake and serum levels were stratified into categories and

the associations were analyzed with Pearson's correlation. The correlation between vitamin D intake and follow-up visits was conducted with regression analysis. Mixed-effects analysis was employed to compare vitamin D intake to BMD and calcium intake to BMD (14). The association between vitamin D and calcium intake and bone health measures was assessed for all participants (n=40). For all analyses, the level of significance was set at $p < 0.05$.

RESULTS

Demographic data for the study population are presented in Table 1. Subjects (n=40) consisted of 22 males (55%) and 18 females (45%). Patients ranged in age between 0 and 165 months. The median age was 18.6 months and the mean age was 10.0 months. The subject population age was slightly skewed to the right due to a patient who was 165 months at the time of visit. Inclusion of this outlier in the analysis did not significantly affect the results. The majority of patients classified themselves as White, Non-Hispanic. Data were collected for 98 visits, of those, there were 40 initial 3-day diet records, 14 25-OH D_3 tests, 80 total body bone mineral density DEXA scans, and 63 serum calcium levels. There were data from follow-up visits for 24 patients. The age of patients at follow-up visits ranged from 3.38 to 81.47 months (mean 23.49 months).

Three-day food diet records were analyzed for vitamin D and calcium intakes. Vitamin D intake from the initial visit was compared to the recommended value from the AAP (400 IU). Seventy-five percent of patients had an inadequate vitamin D intake at the first visit. Baseline vitamin D intake data for 40 initial visits are presented in Table 2. Vitamin D intake was plotted over 3 years for those patients with follow-up visits. There was not a clear pattern of vitamin D intake over time between patients. Vitamin D intake did improve over time; however, this relationship was not strongly correlated ($r=0.23$, $p=0.0021$).

Table 1. Subject Demographic Data

Subject Profile	
Age	**Months**
Range	0.0-165.0
Mean	18.6
Median	10.0
Gender	**(%)**
Male	55.0 (n=22)
Female	45.0 (n=18)
Ethnicity	**(%)**
White/Non-Hispanic	90.0 (n=36)
Other	10.0 (n=4)

Table 2. Vitamin D Intake at Baseline

Category	Participants (%) (n=40)
Inadequate [a]	75.0 (n=30)
Optimal [b]	22.5 (n=9)
Possible Toxicity [c]	2.5 (n=1)

a <400 IU/day b 400-2000 IU/day c >2000 IU/day

Fourteen subjects had a serum 25-OH D_3 level taken during the same visit that a diet record was available. For this subgroup, only one subject had an inadequate serum level (<29.9 ng/mL). Seventy-one percent of patients in the subgroup (n=10) had a serum vitamin D level within the optimal or high range (> 40 ng/mL). The rest were in the low normal range. A higher vitamin D intake was associated with an elevated serum level. However, when these two sets of values were stratified into categories, the two measures did not correlate (Figure 1). Half of the patients with optimal serum levels had an inadequate intake, and twenty nine percent of patients consuming an optimal intake had a serum level that was classified as high.

The result of each DEXA scan was compared with a vitamin D intake and a calcium intake from the same visit. Data from 80 visits were analyzed for vitamin D intake and 76 visits for calcium intake. The correlation between vitamin D intake and bone mineral density was significant ($r=0.31$ $p=0.04$). The same was true for calcium intake and bone mineral density ($r=0.53$ $p=0.01$) (Figures 2 and 3).

There were only five serum vitamin D levels that corresponded with a bone mineral density value; therefore, the sample size was too small to conduct a reliable analysis. Calcium serum levels were too tightly ranged (9-10.7mg/dL), with limited variation, to show a correlation with bone mineral density.

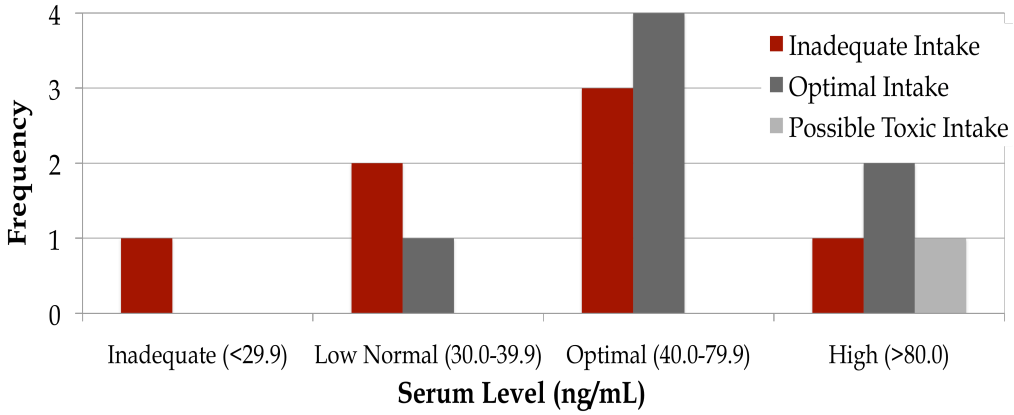

Figure 1. Frequency of vitamin D Intake by corresponding serum level (n=14)

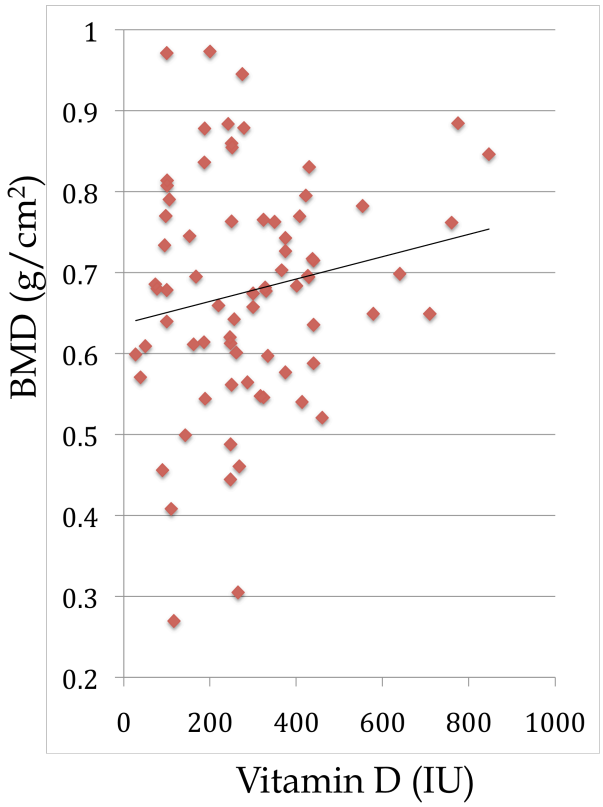

Figure 2. Correlation between vitamin D intake (IU) and bone mineral density (g/cm^2) (n=80) (r=0.31, p=0.04)

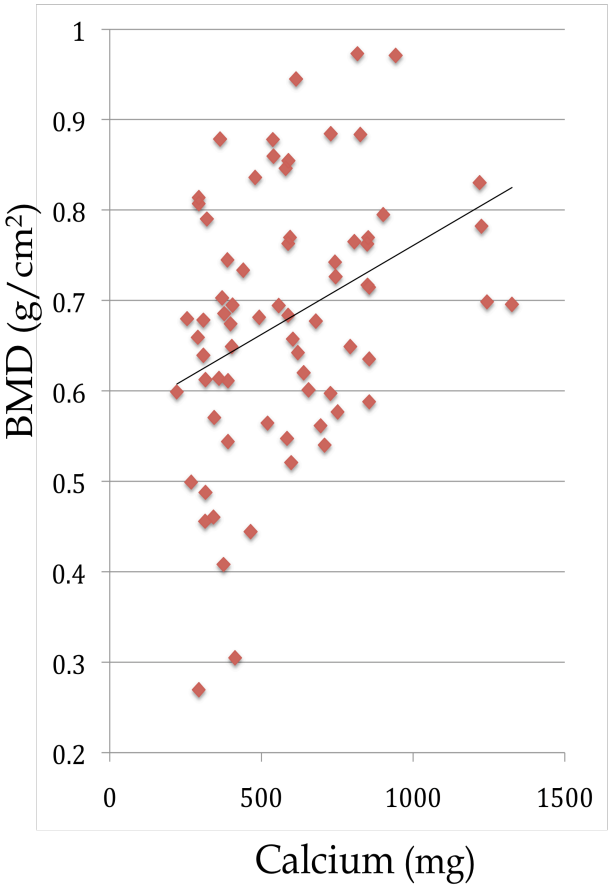

Figure 3. Correlation between calcium intake (mg) and bone mineral density (g/cm^2) (n=76) (r=0.53, p=0.01)

DISCUSSION

Overall, the results from this observational study supported the hypothesis that SMA Type I patients are at risk for nutrient deficiencies. SMA Type I patients have a lower metabolic rate due to decreased lean muscle mass and limited movement (6). Therefore, for this type of SMA, patients require fewer calories per day than their healthy age-matched peers (6). With decreased caloric intake, achieving adequate micronutrient intake can be difficult. The majority of patients in this study (75%) had inadequate intakes of vitamin D at baseline. Despite receiving food record analysis feedback, improvement in vitamin D intake was only slightly correlated with time ($r=0.23$ $p=0.0021$). Some patients increased their vitamin D intake in the 3 years following their initial visit; others decreased or maintained their intake of vitamin D. Barriers to obtaining an adequate amount of vitamin D also included: lack of sun exposure due to geographic location, limited time outside, or increased use of sunscreen (15). Another barrier specific to the SMA population is the use of anticonvulsant drugs such as valproic acid/carnitine, sodium phenylbuterate, and hydroxyurea, which can interfere with the absorption of vitamin D (8).

A serum vitamin D test was collected from a subset of patients ($n=14$). There was only one patient with multiple serum levels. In this case, only the initial level was used for analysis. Serum vitamin D levels and vitamin D intake were strongly correlated ($r=0.65$). However, when serum and intake levels were stratified into categories, the two measures did not correlate. This lack of significance was likely due to a small sample

size. For example, six patients within the subset had inadequate intake, 50% (n=3) had optimal blood levels.

The majority of serum levels (71%, n=10) were optimal or high (>40 ng/mL). A possible explanation for this result is that biological vitamin D levels were not tested until later in the study when there was greater media coverage of the health benefits of vitamin D (16). The first serum test was conducted in 2007, 6 years after data collection began. Clinicians and parents may have had better awareness of the role of the vitamin and the incidence of deficiency and, therefore, were more likely to supplement. Another explanation for the majority of serum levels falling in the optimal-high range is season. In a vitamin D study, winter was one factor of low vitamin D status in children 5-14 years old (17). Seventy-one percent (n=10) of blood tests were drawn between April and October, which represents a time of potentially greater sun exposure for study participants.

Calcium and vitamin D intakes from 80 visits were individually compared to corresponding BMD scores. DEXA scans and food records were matched as closely as possible by date. Most DEXA scans and food records were recorded at the same visit. In three instances a DEXA scan was not conducted at the same visit that a food record was received. BMD is a long-term measure of calcium and vitamin D intake. Therefore, we assumed that a DEXA scan would reflect micronutrient intake.

A stronger correlation exists between calcium intake and BMD ($r=0.53$, $p=0.1$) than vitamin D intake and BMD ($r=0.31$, $p=0.4$). This result was expected because calcium has a direct effect on bone mineralization, while vitamin D has an indirect effect (15). As expected, improvements in vitamin D and calcium intake were associated with

an increase in BMD. The same results were reflected in studies conducted with healthy individuals (18, 19, 20). Attenuating BMD increases the risk of fracture, scoliosis, and osteoporosis. A reference value has not been established for this age range and population; therefore, a statistical analysis of BMD compared to normal values was not conducted.

Serum calcium is not a good measure of calcium status because the body is very efficient in regulating levels to a tight range. Serum calcium does not reflect calcium intake or bone health (15). This statement was evidenced by the limited variance observed in serum calcium levels (9-10.7mg/dL). For this reason, statistical analysis was not performed to compare serum calcium and BMD or calcium intake.

The sample of vitamin D serum levels was too small to make a reliable comparison to BMD. We chose to include this subset of patients to observe preliminary vitamin D status in this population. In future studies, obtaining a 25-OH D_3 level for each subject would be beneficial for determining if vitamin D intake is optimal. BMD is one functional measure of vitamin D intake, although the test is neither specific nor sensitive. Other studies have established a relationship between 25-hydroxy serum levels and BMD of adolescent women (18, 21). Vitamin D serum levels are reflective of vitamin D intake as the majority of biological vitamin D is pooled in the blood (15).

A strength of this study is the methodology for data collection. A 3-day dietary record is a validated measure for assessing intake, particularly for this population (11). SMA Type I patients require 24-hour care, consequently a parent or caregiver can record intake for the child at regular intervals throughout the day; this is likely to increase accuracy. More recently an evaluation of the food record by a registered dietitian who

specializes in SMA provides an incentive to parents who are likely motivated to find the best dietary management for their children. A blood test is an accurate method of assessing dietary intake of vitamin D (15). The test is used exclusively in clinical settings to measure the adequacy of a patient diet for vitamin D. A DEXA scan is used clinically to diagnose poor bone mineral density; the scan is the most valid and reliable measure available (12, 13).

This was an observational design; therefore, the study lacked power compared to an experimental study. The objective of this study was not to impose a dietary intervention, but rather to observe current dietary practices among the SMA population. Another limitation of this study was the lack of vitamin D serum data for all participants with a food record. We chose to include a subset of subjects who did receive a blood test, because this measure is a practical application for assessing vitamin D adequacy in the diet.

CONCLUSION

Nutrition plays a vital role in the quality of life and outcome of spinal muscular atrophy (2, 22). Despite this role, there is very little evidence-based research to support a recommendation for dietary management in this population. In fact, most SMA patients do not have access to a registered dietitian, much less one who specializes in SMA. Parents and caregivers are responsible for choosing a diet for the patient themselves (22).

This study aimed to observe dietary practices of SMA Type I children. The results supported the hypothesis that Type I patients are at risk for nutrient deficiencies due to decreased caloric intake (6). However, inadequate intakes of vitamin D were not reflected in corresponding serum levels in our small subset of patients. When making a recommendation for this population, caloric and micronutrient intake are equally important. Nutrient supplementation may be necessary if appropriate nutrient intake cannot be met while adhering to restricted calories. Further prospective studies will be necessary to determine optimal intakes of vitamin D and calcium in the SMA Type I population.

APPENDIX

THREE-DAY FOOD RECORD

Subject Unique ID (Not Study ID)		
Subject's Name		
Person Filling Out Form		
Relationship to Patient		
Height Feet		
Height Inches		
Height Cm		
Weight Pounds		
Weight Oz		
Weight Kg		
Child's current feeds		
Child's Age	years	months

	Name	Amount
Special Formula Ingredients		
Special Formula Ingredient	1	
Supplements		
Additional Supplement	1	
Food Record Day 1	1	
Date:	2	
Food Record Day 2	1	
Date:	2	
Food Record Day 3	1	
Date:	2	

Breast Feeding		
Day 1	Date:	
Day 1 Pre Weight	kg	
	lbs	oz
Day 1 Post Weight	kg	
	lbs	oz
Day 1 Duration Feeding		

REFERENCES

1. Lunn MR, Wang CH. Spinal Muscular Atrophy. *The Lancet.* 2008;371:2120-2133.

2. Swaboda KJ. Seize the Day: Newborn Screening for SMA. *Am J Med Genet.* 2010;152A:1605-1607.

3. Tsirikos AI, Baker ADL. Spinal Muscular Atrophy: Classification, Aetiology and Treatment of Spinal Deformity in Children and Adolescents. *Current Orthopaedics.* 2006;20:430-445.

4. Tein I, Sloane AE, Donner EJ, Lehotay DC, Millington DS, Kelley RI. Fatty Acid Oxidation Abnormalities in Childhood-Onset Spinal Muscular Atrophy: Primary or Secondary Defect(s)?. *Pediatr Neurol* 1995;12:21-30.

5. Iannacconne ST. Modern Management of Spinal Muscular Atrophy. *J Child Neurol*. 2007;22:974-978.

6. Tilton AH, Miller MD, Khoshoo V. Nutrition and Swallowing in Pediatric Neuromuscular Patients. *Seminars in Pediatric Neurology.* 1998;5:106-115.

7. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *J Child Neuro.* 2007;22:1027-1049.

8. Pronsky ZM. *Food Medication Interactions 15th Edition.* Birchrunville, PA: Food Medication Interactions;2008:304.

9. Wagner Cl, Greer FR. Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents. *Am Acad Ped*. 2008;1862:1142-1152.

10. Shanmugarajan S, Tsuruga E, Swoboda KJ, Maria BL, Ries WL, Reddy SV. Bone Loss in Survival Motor Neuron (Smn-/-SMN2) Genetic Mouse Model of Spinal Muscular Atrophy. *J Patho.* 2009;219:52-60.

11. Tremblay A, Sevigny J, Leblanc C, Bouchard C. The Reproducibility of a Three-day Dietary Record. *Nutr Research.* 1983;3:819-830.

12. Maddalozzo GF, Cardinal BJ, Snow CM. Concurrent Validity of the BOD POD and Dual Energy X-ray Absorptiometry Techniques for Assessing Body Composition in Young Women. *J Am Diet Assoc.* 2002;102:1677-1679.

13. Kanda F, Fujii Y, Takahashi K, Fujita T. Dual-Energy X-ray Absorptiometry in Neuromuscular Diseases. *Muscle and Nerve*. 1994;17:431-435.

14. SAS Statistical Analysis Software (version 9.1.2, 2010, SAS Institute Inc., Cary, NC, USA).

15. Gropper SS, Smith JL, Groff JL. *Advanced Nutrition and Human Metabolism Fifth Addition.* Bellmont, CA: Wadsworth. 2009;395-398.

16. Dietary Reference Intakes for Calcium and Vitamin D. *Institute of Medicine of the National Academy of Science.* 2011.

17. Rockwell JE, Green TJ, Skeaff CM, Whiting SJ, Taylor RW, Williams SM, Parnell WR, Scragg R, Wilson N, Schaff D, Fitzgerald ED, Wohlers MW. Season and Ethnicity Are Determinants of Serum 25-Hydroxyvitamin D Concentrations in New Zealand Children Aged 5-14 y. *J Nutr*. 2005;135:2602-2608.

18. Bischoff–Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive Association Between 25-hydroxy Vitamin D Levels and Bone Mineral Density: A Population-Based Study of Younger and Older Adults. *Am J Med*. 2004;116:634-639.

19. Dawson-Hughes B, Harris SS. Krall EA, Dallal GE, Falconer G, Green CL. Rates of Bone Loss in Premenopasaul Women Randomly Assigned to One of Two Dosages of Vitamin D. *J Clin Nutr.* 1995;61:1140-1145.

20. Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of Vitamin D Supplementation of Wintertime and Overall Bone Loss in Healthy Postmenopasaul Women. *Ann Intern Med.* 1991;115:505-512.

21. Outila TA, Karkkainen MUM, Lamber-Allardt CJE. Vitmain D Status Affects Serum Parathyroid Hormone Concentrations During Winter in Female Adolescents: Associations with Forearm Bone Mineral Density. Am J Clin Nutr. 2001;74:206-210.

22. Poruk KE, Davis RH, Smart A, Chisum B, LaSalle B, Chan GM, Gill G, Reyna SP, Swoboda KJ. Nutritional Analysis in Infants and Children with Spinal Muscular Atrophy Type I. *Unpublished.* 2010.

23. SMA and Nutrition. http://smaandnutrition.org/home.php. Accessed November 20, 2010.